

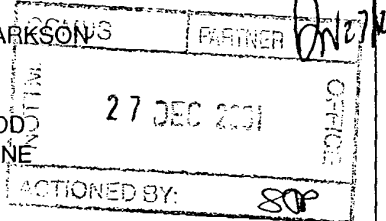
PATENT COOPERATION TREATY

not entered

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing
(day/month/year) 21.12.2001

Applicant's or agent's file reference
IMPY/P23285PC

IMPORTANT NOTIFICATION

International application No.
PCT/GB00/03265

International filing date (day/month/year)
25/08/2000

Priority date (day/month/year)
25/08/1999

Applicant
IMPERIAL CANCER RESEARCH TECHNOLOGY LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference IMPY/P23285PC	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB00/03265	International filing date (day/month/year) 25/08/2000	Priority date (day/month/year) 25/08/1999
International Patent Classification (IPC) or national classification and IPC C07K7/00		
Applicant IMPERIAL CANCER RESEARCH TECHNOLOGY LIMITED et al.		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 11 sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none">I <input checked="" type="checkbox"/> Basis of the reportII <input type="checkbox"/> PriorityIII <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicabilityIV <input type="checkbox"/> Lack of unity of inventionV <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statementVI <input checked="" type="checkbox"/> Certain documents citedVII <input type="checkbox"/> Certain defects in the international applicationVIII <input checked="" type="checkbox"/> Certain observations on the international application		
Date of submission of the demand 21/03/2001	Date of completion of this report 21.12.2001	
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Masturzo, P Telephone No. +31 70 340 2275	



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB00/03261

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-136 as originally filed

Claims, No.:

1-50 as received on 29/11/2001 with letter of 28/11/2001

Drawings, sheets:

1/30-30/30 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB00/03261

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 27-43.

because:

☒ the said international application, or the said claims Nos. 29-31,34-36 and 40-43 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 27,32-43 are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)

Yes: Claims 1-50

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB00/03265

	No:	Claims	
Inventive step (IS)	Yes:	Claims	2-50
	No:	Claims	1
Industrial applicability (IA)	Yes:	Claims	1-28, 32-33, 37-39, 44-50
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/03265

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 27 and 32-43 are (at least partially) defined only through the functional feature to be identifiable through the method of claims 26 and 49 and to be able to interact with SMAD. This did not permit a complete search to be carried out due to the vagueness of the subject. The above claims have been searched only insofar as defined in the description as real examples.

Claims 29-31, 34-36 and 40-43 relate to subject-matter considered by this Authority to be covered (at least partially) by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1: Bioch. Biophys. Res. Comm. 252, pages 257-262 (1998);
- D2: J. Gen. Virol. 73, pages 2625-2630 (1992);
- D3: CA 128:281957 (1998);
- D4: WO-A-9614416 (Pierre Fabre);
- D5: WO-A-9730074 (University of North Carolina & Cytogen);
- D6: FR-A-2766192 (Pierre Fabre);
- D7: Molecular Cell 2, pages 109-120 (1998).

1) Claims 1-50 are now recognized as novel under Art. 33(2) PCT.

2) D7 is the considered to represent the best prior art for claims 1-26, 28-31, 32-43 (partially), 44-50. It discloses complexes of SMAD 2 and SMAD 3 with the DNA-binding protein FAST 2, which regulate TGF- β dependent transcription. The difference between

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/03265

D7 and the present application is considered to reside in the fact that no small activators of SMAD, comprising the yet unidentified SIM (SMAD interaction motif) are disclosed. The objective problem is considered to reside in the identification of small SMAD interacting molecules, which can regulate TGF- β depending transcription. The applicant has disclosed a series of SMAD-interacting compounds, which possess a regulatory ability towards the TGF- β depending transcription (see i. a. example 3 and figure 9). Therefore it may be assumed that for claims 2-26, 28-43 (these partially) and 44-50 the presence of an inventive step under Art. 33(3) PCT is demonstrated. However, the applicant provides only scant proof that the wide class of compounds containing the short sequence PP(T/N)K or three residues thereof (claim 4) and less than 32 residues can in general exert the effect of regulating TGF- β induced translation. Therefore an inventive step under Art. 33(3) PCT cannot be recognized for the broad claim 1 for plausibility reasons.

Re Item VI

Certain documents cited

WO-A-35407 (Temple University)	22-6-2000	16-12-1998
WO-A-64945 (Babraham Institute)	2-11-2000	22-4-1999
WO-A-0043494 (Scripps Res. Institute)	27-7-2000	26-1-1999

Re Item VIII

Certain observations on the international application

Claims 1, referring to peptides of less than 32 residues in length, cannot represent the independent claim for claims 8-9 and 11, dealing with longer peptides, and moreover rather obscure in nature (the use of the generic word "interacting polypeptide" makes it unclear whether it is referred to the one containing SIM or whatever else).

(1) and where the interacting polypeptide is not
 a kininogen or fragment thereof; or the glycoprotein
 of human respiratory syncytial virus or fragment
 thereof; or a fibroblast growth factor receptor (FGFR)
 on the peptide SKPTTKQRQNKPPNKP

CLAIMS

1. A polypeptide (interacting polypeptide) capable of interacting with a Smad polypeptide wherein the interacting polypeptide comprises a Smad Interaction Motif (SIM) and is less than 32 amino acids in length.

2. A polypeptide capable of interacting with a Smad polypeptide wherein the interacting polypeptide comprises the amino acid sequence PP(T/N)K and is less than 32 amino acids in length.

~~3. A polypeptide comprising the amino acid sequence PP(T/N)K that is less than 32 amino acids in length.~~

3 4. A polypeptide capable of interacting with a Smad polypeptide wherein the interacting polypeptide comprises a Smad Interaction Motif (SIM), for example the amino acid sequence PP(T/N)K or three out of four residues thereof, and is not full-length *Xenopus* or human FAST1 or a fragment thereof, mouse FAST2, *Xenopus* Milk, *Xenopus* Mixer, *Xenopus* Bix3 or Bix2.

20 75. The polypeptide of claim 1, or 4 wherein the SIM comprises at least 8, 9 or 10 of the specified residues (ie not residues designated by an X) of the amino acid sequence D/E-Hyd-(X)_n-P-P-(N/T)-K-(T/S)-(I/V)-(X)_m-(D/E)-(M/V/I)-(X)_k-P

wherein m= 0 to 7; k= 0 to 8 or 12; n = 0 to 15 or 18.

8 9 10 6. The polypeptide of claim 1, 2, 4 or 5 wherein the Smad polypeptide is Smad2 or Smad3.

<2> and is a transcription factor or
fragment thereof
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CLAIMS

- 4 1. A polypeptide (interacting polypeptide) capable of interacting with a Smad polypeptide wherein the interacting polypeptide comprises a Smad Interaction Motif (SIM) and is less than 32 amino acids in length.^{<2>}
- 5 2. A polypeptide capable of interacting with a Smad polypeptide wherein the interacting polypeptide comprises the amino acid sequence PP(T/N)K^{<2>} and is less than 32 amino acids in length.^{<2>}
- 10 ~~3. A polypeptide comprising the amino acid sequence PP(T/N)K that is less than 32 amino acids in length.~~
- 6 4. A polypeptide capable of interacting with a Smad polypeptide wherein the interacting polypeptide comprises a Smad Interaction Motif (SIM), for example the amino acid sequence PP(T/N)K or three out of four residues thereof, and is not full-length *Xenopus* or human FAST1 or a fragment thereof, mouse FAST2, *Xenopus* Milk, *Xenopus* Mixer, *Xenopus* Bix3 or Bix2.^{<2>}
- 20 ~~5. The polypeptide of claim 1 or 4 wherein the SIM comprises at least 8, 9 or 10 of the specified residues (ie not residues designated by an X) of the amino acid sequence D/E-Hyd(X)_n-P-P-(N/T)-K-(T/S)-(I/V)-(X)_m-(D/E)-(M/V/I)-(X)_k-P wherein m= 0 to 7; k= 0 to 8 or 12; n = 0 to 15 or 18.~~
- 25 6. The polypeptide of claim 1, 2, 4 or 5 wherein the Smad polypeptide is Smad2 or Smad3.

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^{interacting} 11 ^{3, 7 to 10 interacting} 7. The polypeptide of any one of claims 1 to 6 wherein the polypeptide is a transcription factor or a fragment thereof.

^{interacting} 5 ^{3, 6 or 7 interacting} 8. The polypeptide of ~~any one of claims 4 to 7~~ wherein the polypeptide is less than 100 amino acids in length.

^{interacting} 9 ^{of claim 8} 9. The polypeptide of ~~any of the preceding claims~~ wherein the polypeptide is between 4 and about 30 or 35 amino acids in length.

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12 10. The polypeptide of any of the preceding claims wherein an acidic amino acid residue is present at a position from 3 to 10 residues C-terminal of the amino acid sequence PP(T/N)K or amino acid sequence corresponding to the PP(T/N)K motif and/or a proline residue is present at a position from 5 to 20 residues C-terminal of the amino acid sequence PP(T/N)K K or amino acid sequence corresponding to the PP(T/N)K motif.

13 11. The polypeptide of any of the preceding claims comprising the amino acid sequence PPNKTITPDMNVRIPPI or PPNKTITPDMNTIIPQI or
 20 PPNKSVFDVLTSHPGD or PPNKSIYDVWVSHPRD or
 PPNKSIYDVWVSHPRD or PPNKTVFDIPVYTGHPG or
 PPNKTITPDMNTIIPQI or PPNKTIGPEMKVVIPL or PPNKSSKRGNTPPW
 or LLMDFNFPNKTITPDMNVRIPPI or
 HSNLMMDFPNKTITPDMNTIIPQI or
 25 LDNMLRAMPPNKSVDVLTSHPGD or
 LDSLFQGVPPNKSIVDVWVSHPRD or
 LDALFQGVPPNKSIVDVWVSHPRD or

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LKNAPSDFPPNKTVFDIPVYTGHGP or HSNLVMEFPPNKTITPDMNTIIPQI
 or LVEYDNFPPNKTIGPEMKVVIPPL or
 ITSDAYSDESCPPPNKSSKRGNTPPW.

514-12. A polypeptide consisting of the amino acid sequence

PPNKTITPDMNVRIPPI or PPNKTITPDMNTIIPQI or
 PPNKSVFDVLTSHPGD or PPNKSIYDVWVSHPRD or
 PPNKSIYDVWVSHPRD or PPNKTVFDIPVYTGHGP or
 PPNKTITPDMNTIIPQI or PPNKTIGPEMKVVIPPL or PPNKSSKRGNTPPW

10 or LLMDFNFFPPNKTITPDMNVRIPPI or
 HSNLMMDFFPPNKTITPDMNTIIPQI or
 LDNMLRAMPPNKSVDVLTSHPGD or
 LDSLFQGVPPNKSIVDVWVSHPRD or
 LDALFQGVPPNKSIVDVWVSHPRD or
 15 LKNAPSDFPPNKTVFDIPVYTGHGP or HSNLVMEFPPNKTITPDMNTIIPQI
 or LVEYDNFPPNKTIGPEMKVVIPPL or
 ITSDAYSDESCPPPNKSSKRGNTPPW.

15-13. The polypeptide of any of the preceding claims comprising the amino acid
 20 sequence of residues 283 to 307 of Mixer.

16-14. The polypeptide of any of the preceding claims wherein the said polypeptide
 is a peptidomimetic compound.

17
 25 15. A molecule comprising a polypeptide as defined in any of Claims 1 to 14 and
 a further portion, wherein the said molecule is not full-length *Xenopus* or human

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FAST1 or a fragment thereof, mouse FAST2, *Xenopus* Milk, *Xenopus* Mixer or *Xenopus* Bix2.

¹⁸
16. A molecule according to claim ¹⁴~~15~~ wherein the molecule is

5 Biotin.Aminohexanoicacid-

RQIKIWFQNRRMKWKKLLMDFNNFPPNKTITPDMNVRIPPI

or

5-FAM-AMINOHEXANOICACID-

RQIKIWFQNRRMKWKKPEVKNA PKDFPPNKT VFDIPVYTGH PGFLA

10 ¹⁹
~~17~~. A nucleic acid encoding or capable of expressing a polypeptide or molecule according to any one of claims ¹⁸~~1~~ to ~~16~~.

²⁰ ~~18~~. A nucleic acid complementary to a nucleic acid encoding a polypeptide according to any one of claims ¹⁵~~1~~ to ~~13~~.

²¹ ~~19~~. An antibody capable of reacting with a polypeptide according to any one of claims ¹⁶~~1~~ to ~~14~~.

²²
20 ~~20~~. A method of identifying a polypeptide that is capable of interacting with a Smad polypeptide, comprising examining the sequence of a polypeptide and determining that the polypeptide comprises a Smad Interaction Motif (SIM), for example the amino acid sequence PP(T/N)K or three out of four residues thereof.

25 ²³
~~21~~. The method of claim ²²~~20~~ comprising determining that the polypeptide comprises at least 8, 9 or 10 of the specified residues (ie not residues designated

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by an X) of the amino acid sequence D/E-Hyd-(X)_n-P-P-(N/T)-K-(T/S)-(I/V)-
(X)_m-(D/E)-(M/V/I)-(X)_k-P

wherein m = 0 to 7; k = 0 to 8 or 12; n = 0 to 15 or 18.

- 24
5 ~~22~~. The method of claim ~~20~~ or ~~21~~ comprising determining that the polypeptide comprises the amino acid sequence PP(T/N)K.

- 25
23. The method of claim ~~20~~, ~~21~~ or ~~22~~ further comprising determining that an
acid amino acid residue is present at a position from 3 to 10 residues C-terminal
10 of the amino acid sequence PP(T/N)K or amino acid sequence corresponding to
the PP(T/N)K motif, and/or a proline residue is present at a position from 5 to
20 residues C-terminal of the amino acid sequence PP(T/N)K or amino acid
sequence corresponding to the PP(T/N)K motif.

- 25
15 ~~24~~. A method of identifying a compound capable of disrupting or preventing the
interaction between a Smad polypeptide and a target polypeptide that is (1) a
transcription factor capable of interacting with the said Smad polypeptide and/or
(2) a polypeptide capable of interacting with the said Smad polypeptide, the
interaction requiring α -helix2 of the said Smad polypeptide or (3) a polypeptide
20 comprising the amino acid sequence PP(T/N)K, the method comprising
measuring the ability of the compound to disrupt or prevent the interaction
between the Smad polypeptide and a polypeptide or molecule according to any
one of claims 1 to ~~16~~.¹⁸

- 27
25 ~~25~~. A compound identified by or identifiable by the method of claim ~~24~~ or claim
49
47.

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26. A kit of parts comprising a Smad polypeptide and a polypeptide or molecule according to any one of claims 1 to ¹⁸16.

27. A method of disrupting or preventing the interaction between a Smad polypeptide and a target polypeptide that is (1) a transcription factor capable of interacting with the said Smad polypeptide and/or (2) a polypeptide capable of interacting with the said Smad polypeptide, the interaction requiring α -helix² of the said Smad polypeptide, the method comprising exposing the Smad polypeptide to a polypeptide or molecule according to any one of claims 1 to ¹⁸16 or to an antibody according to claim ²¹19 or to a compound according to claim ²⁷25.

28. A method of disrupting or preventing the interaction between a Smad polypeptide and a polypeptide comprising the amino acid sequence PP(T/N)K wherein the Smad polypeptide is exposed to a polypeptide or molecule according to any one of claims 1 to ¹⁸16 or to an antibody according to claim ²¹19 or to a compound according to claim ²⁷25.

29. The method of claim ²⁹27 or ³⁰28 wherein the Smad polypeptide is Smad2 or Smad3.

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30. A compound according to claim ²⁷25 or polypeptide or molecule according to any one of claims 1 to ¹⁸16 or nucleic acid according to claim ¹⁹17 or ²⁰18 or antibody according to claim ¹³19 for use in medicine.

31. A method of modulating activin or TGF β signalling in a cell *in vitro* wherein the cell is exposed to a polypeptide, molecule, compound, nucleic acid or antibody as defined in claim ³²30.

³⁴
~~32~~. A method of modulating activin or TGF β signalling in a cell *in vivo* wherein the cell is exposed is exposed to a polypeptide, molecule, compound, nucleic acid or antibody as defined in claim ~~30~~.³²

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³⁵
~~33~~. The method of claim ~~31~~ or ~~32~~ wherein the cell is a late stage tumour cell.

³⁶

~~34~~. The use of a polypeptide, molecule, compound, nucleic acid or antibody as defined in claim ~~30~~ in the manufacture of a medicament for treatment of a patient in need of modulation of activin or TGF β signalling.

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³⁷

~~35~~. The use of a polypeptide, molecule, compound, nucleic acid or antibody as defined in claim ~~30~~ in the manufacture of a medicament for treatment of a patient with cancer.

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³⁸

~~36~~. The use of a polypeptide, molecule, compound, nucleic acid or antibody as defined in claim ~~30~~ in the manufacture of a medicament for treatment of a patient in need of reducing extracellular matrix deposition, encouraging tissue repair and/or regeneration, tissue remodelling or healing of a wound, injury or surgery, or reducing scar tissue formation arising from injury to the brain.

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~~37~~. The use of a polypeptide, molecule, compound, nucleic acid or antibody as defined in claim ~~30~~ in the manufacture of a medicament for treatment of a patient with or at risk of end-stage organ failure, pathologic extracellular matrix accumulation, a fibrotic condition, disease states associated with immunosuppression (such as different forms of malignancy, chronic degenerative diseases, and AIDS), diabetic nephropathy, tumour growth, kidney damage (for

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example obstructive neuropathy, IgA nephropathy or non-inflammatory renal disease) or renal fibrosis.

~~40~~

- ~~38~~. A method of treating a patient in need of modulation of activin or TGF β signalling, the method comprising administering to the patient an effective amount of a polypeptide, molecule, compound, nucleic acid or antibody as defined in Claim ~~30~~.³²

~~41~~

- ~~39~~. A method of treating a patient with cancer the method comprising administering to the patient an effective amount of a polypeptide, molecule, compound, nucleic acid or antibody as defined in Claim ~~30~~.³²

~~42~~

- ~~40~~. A method of reducing extracellular matrix deposition or encouraging tissue repair and/or regeneration, or tissue remodelling or healing of a wound, injury or surgery, or reducing scar tissue formation arising from injury to the brain, the method comprising administering for the patient an effective amount of a polypeptide, molecule, compound, nucleic acid or antibody as defined in Claim ~~30~~.³²

~~43~~

- ~~41~~. A method of treating a disease or condition as defined in Claim ~~37~~.³⁹ the method comprising administering to the patient an effective amount of a polypeptide, molecule, compound, nucleic acid or antibody as defined in Claim ~~30~~.³²

~~44~~

- ~~42~~. A substantially pure complex comprising (1) a Smad2 or Smad3 polypeptide, (2) a Smad4 polypeptide and (3) a Mixer and/or Milk and/or Bix2/3 and/or FAST3 polypeptide.

⁴⁵
~~43~~. A preparation comprising (1) Smad2 or Smad3 polypeptide, (2) a Smad4 polypeptide and (3) a Mixer and/or Milk and/or Bix2/3 and/or FAST3 polypeptide (in the form of a complex or otherwise) when combined with other
 5 components *ex vivo*, said other components not being all of the components found in the cell in which said (1) Smad2 or Smad3 polypeptide, (2) a Smad4 polypeptide and (3) a Mixer and/or Milk and/or Bix2/3 and/or FAST3 polypeptide (in the form of a complex or otherwise) are naturally found.

⁴⁶
 10 ~~44~~. A cell comprising 1) a recombinant polynucleotide suitable for expressing a transcription factor that is capable of interacting with a Smad polypeptide and 2) a recombinant polynucleotide comprising a reporter gene driven by a promoter with a binding site for the said transcription factor.

⁴⁷
 15 ~~45~~. A stable cell line cell comprising a reporter gene driven by a promoter with one or more binding sites for an activated Smad, wherein the Smad is activated in the cell by exposure of the cell to TGF β .

⁴⁸ ^{46 47}
 20 ~~46~~. The cell according to claim ~~44~~ or ~~45~~ wherein the reporter gene expresses luciferase, secreted alkaline phosphatase (SEAP), CAT or a green fluorescent protein (GFP).

⁴⁹
 25 ~~47~~. A method of identifying a compound capable of modulating TGF β -dependent transcription wherein the effect of the compound on expression of the reporter gene in a cell according to claim ^{46 47 48} ~~44~~, ~~45~~ or ~~46~~ is measured, following treatment of the cell with TGF β .

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48. A method of identifying a compound capable of modulating TGF β -dependent transcription wherein the effect of the compound on TGF β -signalling-dependent invasive behaviour of a stably-transformed cell line cell, for example in collagen gels, is measured and a compound that reduces invasive behaviour is selected.

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49. The method of claim 48 wherein the stably-transformed cell line is a MDCK cell line that is capable of expressing recombinant active Raf-1.

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